



Time Intervals for New Onset Aerodigestive Disorders

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Note: As new scientific information becomes available, the Administrator of the World Trade Center Health Program may modify time intervals for new onset aerodigestive disorders.

Executive Summary

The Administrator of the World Trade Center (WTC) Health Program has determined that no minimum time interval will be applied to five categories of new onset aerodigestive disorders that meet the temporal sequence of symptoms requirement for certification of a WTC-related health condition and that maximum time intervals for the five categories of aerodigestive disorders are as follows:¹

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| Category I | Obstructive airways diseases (OADs) — Maximum Time Interval is 5 years. <ul style="list-style-type: none">▪ Chronic respiratory disorder (fumes/vapors)▪ Asthma▪ Reactive airways dysfunction syndrome (RADS)▪ WTC-exacerbated chronic obstructive pulmonary disease▪ Chronic cough syndrome |
| Category II | Upper respiratory diseases (URDs) — Maximum Time Interval is 5 years. <ul style="list-style-type: none">▪ Upper airway hyperreactivity▪ Chronic rhinosinusitis▪ Chronic nasopharyngitis▪ Chronic laryngitis |
| Category III | All types of interstitial lung disease (ILDs) — No Maximum Time Interval. |
| Category IV | Co-occurring Gastroesophageal reflux disease (GERD) (GERD co-occurring with an aerodigestive disorder in Category I, II, or III) — Maximum Time Interval is 5 years |
| Category V | Isolated GERD (GERD not co-occurring with an aerodigestive disorder in Category I, II, or III) — Maximum Time Interval is 1 year. |

¹ “Sleep apnea exacerbated by or related to a condition described in a previous disease” is included as an aerodigestive disorder on the list of health conditions (42 U.S.C. § 300mm-22(a)(3)(A)(xii)), but the maximum time interval for certification as a WTC-related health condition is not addressed in this document.

I. Introduction

The James Zadroga 9/11 Health and Compensation Act of 2010² ("Act") authorizes treatment for enrolled responders and survivors whose health conditions are certified by the WTC Health Program as WTC-related health conditions. In order for a health condition to be certified, a Clinical Center of Excellence (CCE) or Nationwide Provider Network (NPN) physician must first make a determination that an individual's WTC exposure to airborne toxins, other hazards, or adverse conditions resulting from the September 11, 2001 terrorist attacks (9/11 exposure) is substantially likely to be a significant factor in aggravating, contributing to, or causing an individual's health condition.

The physician's determination is transmitted to the Administrator of the WTC Health Program. If the Administrator finds that the health condition is included on the List of WTC-Related Health Conditions³ and concurs that the 9/11 exposure is substantially likely to be a significant factor in aggravating, contributing to, or causing the health condition, then the Administrator will certify the individual's health condition as eligible for treatment by the WTC Health Program.⁴ The CCE/NPN physician's determination and the Administrator's certification decision must be based on an assessment of the following: (1) the individual's exposure to airborne toxins, any other hazard, or any other adverse condition resulting from the terrorist attacks; and (2) the type of symptoms and temporal sequence of symptoms.⁵

Time Intervals for New Onset Aerodigestive Disorders is the second in a series of WTC Health Program policies that provide information about the temporal sequence of symptoms requirement for determination and certification of WTC-related health conditions. The first policy in the series, "*Minimum Latency & Types or Categories of Cancer*," addresses the temporal sequence for cancers that are considered WTC-related health conditions and is posted on the WTC Health Program website at <http://www.cdc.gov/wtc/policies.html>.

Time Intervals for New Onset Aerodigestive Disorders provides information about the minimum and maximum amount of time allowed between the individual's WTC exposure and the onset of symptoms of an aerodigestive disorder⁶ for purposes of determination and certification of the

² 42 U.S.C. §§ 300mm to 300mm-61.

³ 42 C.F.R. § 88.1.

⁴ 42 U.S.C. 300mm-22(b)(1)(B)(ii).

⁵ 42 U.S.C. § 300mm-22(a)(2).

⁶ The term "aerodigestive disorder" includes the following specific types of WTC-related health conditions: (1) Interstitial lung disease; (2) chronic respiratory disorder—fumes and vapors; (3) asthma; (4) reactive airways dysfunction syndrome (RADS); (5) WTC-exacerbated chronic obstructive pulmonary disease (COPD); (6) chronic cough syndrome; (7) upper airways hyperreactivity; (8) chronic rhinosinusitis; (9) chronic nasopharyngitis; (10) chronic laryngitis; (11) gastroesophageal reflux disorder (GERD); and (12) sleep apnea exacerbated by or related to a condition mentioned in (1) through (11). See 42 U.S.C. § 300mm-22(a)(3)(A) and § 300mm-32(b)(1).

disorder as a WTC-related health condition.⁷ For a WTC-related aerodigestive disorder, the time interval is the period of time between the last day of the individual's 9/11 exposure and the earliest date of symptoms of the aerodigestive disorder under consideration.

For each of the five categories of aerodigestive disorders, the Administrator has determined that no minimum time interval should be established. For four of the five categories of aerodigestive disorders—obstructive airways, upper respiratory diseases, gastroesophageal reflux disease (GERD) co-occurring⁸ with another WTC-related aerodigestive disorder, and isolated GERD⁹—the Administrator has determined that for certification a maximum time interval should not be exceeded unless highly unique exposure circumstances can be documented for that individual. However, for a fifth category, interstitial lung diseases, the Administrator has determined that no maximum time interval can be established. The specific exposure circumstances of each case will be considered in the determination and certification processes to decide whether the maximum time intervals specified in this policy are reasonable to apply to the particular case.

II. Information Sources

The Administrator selected the maximum time intervals for the categories of aerodigestive disorders based on the best available published science and the WTC Health Program's (the Program) clinical experience since 2001. Specifically, the Administrator gathered information to establish the basis for the maximum time intervals from four sources. Source information was evaluated for quality and synthesized to support the selection of maximum time intervals for each of the categories.

The four sources are described in order of preference.

A. Time Interval Source 1: Published Studies of Observed Time Intervals for Aerodigestive Disorders in the WTC-Exposed Cohort

Time Interval Source 1 includes published scientific studies of aerodigestive disorders in WTC-exposed populations and the onset of symptoms of aerodigestive disorders.

B. Time Interval Source 2: Published Studies of Observed Time Intervals for Aerodigestive Disorders in Other Cohorts with Analogous Exposure

⁷ WTC-related health conditions are directly attributed to exposures caused by the September 11, 2001 terrorist attacks. WTC-related health conditions differ from "medically-associated" health conditions which result from the progression or the treatment of a WTC-related health condition. Maximum Time Intervals have not been determined for medically-associated health conditions.

⁸ Co-occurring WTC-related health conditions are two or more WTC-related health conditions that occur during the same time period but are independently associated with exposures caused by the September 11, 2001 terrorist attacks.

⁹ Isolated GERD is WTC-related GERD which does not co-occur with another WTC-related health condition.

Time Interval Source 2 includes published scientific studies on time intervals observed for aerodigestive disorders observed in other cohorts with exposures analogous to the exposures from the September 11, 2001 terrorist attacks.

C. Time Interval Source 3: The WTC Health Program's Clinical Experience since 2001

Time Interval Source 3 includes information not published in the scientific literature but reflects clinical observations from participating WTC Health Program physicians, clinical surveillance information from WTC Health Program Data Centers, and periodic scientific meetings pertaining to time intervals observed for aerodigestive disorders in the WTC-exposed cohort.

D. Time Interval Source 4: Assessment by Analogy to a Similar Health Condition

Time Interval Source 4 includes published scientific studies of aerodigestive disorders with similar pathophysiology to a type of aerodigestive disorder in one of the five categories.

III. Discussion of Time Intervals for Aerodigestive Disorders

Respiratory and gastrointestinal conditions (i.e., aerodigestive disorders) have been frequently identified among individuals who responded to the September 11, 2001, terrorist attacks in New York City (NYC) [Skloot et al. 2004; Herbstman and Schwab 2005; Tapp et al. 2005; Herbert et al. 2006; Buyantseva et al. 2007; Webber et al., 2009] as well as in exposed NYC community residents, children, and office workers [Centers for Disease Control Prevention 2002; Reibman 2003; Szema et al. 2004]. The primary risk factors for aerodigestive disorders in responders are early arrival at the site of the former WTC towers and being caught in the dust cloud on September 11, 2001.

The majority of aerodigestive disorders seen in NYC WTC-exposed individuals are thought to have a common underlying pathophysiology based on mucosal inflammation of the aerodigestive tract [Banauch et al. 2005]. Toxicology studies of NYC WTC agents found in building materials provide a biologically plausible rationale that acute and chronic inflammation led to decreased lung function within months of exposure, followed by the longer-term development of airways obstruction [Gavett 2003,2006; Gavett et al. 2003; Payne et al. 2004]. These changes in lung mechanics and possible changes in lung architecture resulted in the continued need for pulmonary evaluation months to years following NYC WTC exposure [Wieden et al. 2011]. The Program's clinical experience consistently noted that the onset of symptoms of the most common aerodigestive disorders was both acute and delayed.

For each of the five categories, the Administrator has determined that a minimum time interval should not be established because symptoms consistent with health conditions in each category were identified during or shortly after the September 11, 2001 terrorist attacks [Prezant et al. 2002; Rom 2002; Landrigan 2004; Izbicki 2007]. The information available to the Administrator and the bases for selecting maximum time intervals for each category of aerodigestive condition are discussed in the sections below.

A. Category I—Obstructive Airways Diseases

The diseases categorized as obstructive airways diseases (OAD) have common features such as airways obstruction and airway inflammation, may evolve into other diseases within this category, and have similar diagnostic methods and treatment regimens. While these diseases have important physiological differences among them, their shared traits are considered to be more important than their distinctions.¹⁰

Longitudinal studies of NYC WTC responders suggest that the incidence of new-onset respiratory symptoms and diseases and the decline in pulmonary function stabilized within 3 years of exposure to the WTC disaster [Ekenga and Friedman-Jiménez 2011]. The majority of NYC WTC-exposed fire department rescue workers experienced a substantial age-adjusted decline in airflow within the first 12 months after September 11, 2001, followed by a persistent plateau in pulmonary function in the 6 years thereafter [Banauch et al. 2003; Herbert et al. 2006]. The pulmonary diseases consisted mainly of chronic inflammation characterized by airflow obstruction which affected large and small airways. CCE clinicians described the onset of irritant-induced lower airway diseases, such as bronchial disease syndromes, in NYC WTC responders as sometimes relatively slow, and, in many cases, the symptoms were not completely expressed clinically until a few months after leaving the disaster worksite; this experience was reported by De la Hoz et al. [2011]. [*Time Interval Source 1*]

To date, the most thoroughly studied OAD among NYC WTC responders and survivors is asthma. The Administrator has determined that asthma is the best disease to represent the OAD category for selection of a maximum time interval because it has substantial information available in *Time Interval Source 1* and is sufficiently similar in pathophysiology and diagnostic and treatment modalities as the other health conditions in the OAD category.

The rate of asthma diagnosis was markedly elevated among NYC WTC responders in the years following September 11, 2001 [Brackbill et al. 2009; De la Hoz et al. 2008b, 2011; Herbert et al. 2006; Kim et al. 2012]. Wheeler et al. [2007] analyzed 2003–2004 interview data from the World Trade Center Health Registry (Registry) for 25,748 NYC workers who did not have asthma before September, 11, 2001, and compared their results to the expected 3-year risk of asthma, based on the reported incidence of asthma in the general adult population of 100/100,000 person-years. A total of 926 of these workers in the Registry reported being told they had asthma for the first time after September, 11, 2001, which is a 3-year risk of 3.6% and is 12 times greater than the risk in the general adult population. [*Time Interval Source 1*]

The annualized rate of asthma diagnoses among the diversely-exposed group including NYC WTC responders, Lower Manhattan residents and office workers, and passersby on

¹⁰ Memorandum from World Trade Center Data Center Directors to CAPT Dori Reissman, M.D., Associate Administrator, WTC Program. *Rationale for an OAD Category Inclusive of COPD and Emphysema ICD9 Codes*. June 8, 2012. On file in the WTC Health Program Office, Washington, D.C.

September 11, 2001, was at least six times greater in the four months immediately following the attacks than the estimated annual national adult rate of 0.5% for 2002 [Brackbill et al. 2009]. Also, for each of the four years after 2001 (2002–2005) the prevalence of 12-month asthma increased among a group comprised of only NYC WTC responders, when compared to the national estimate based on the National Health Interview Survey (NHIS)¹¹. The increase in prevalence indicates that new cases of asthma were being identified during these years. The lifetime asthma prevalence continued to increase for six years [Kim et al. 2012]. The reported lifetime asthma prevalence included any history of asthma which encompasses time before the 9/11 exposures and may be subject to recall bias. Also, the questionnaire for the WTC cohort included cough variant asthma and reactive airways dysfunction syndrome, which were not included in the NHIS survey.

For these reasons, the Administrator considers lifetime prevalence of asthma a less reliable measure for new onset asthma. By contrast, among the more diversely-exposed group, the 3-year asthma diagnosis rate from 2004-2007 was 1.3% for those who reported no symptoms at their initial monitoring exam, which is similar to the expected rate if the September 11, 2001, terrorist attacks had not happened [Brackbill et al. 2009]. [*Time Interval Source 1*]

Therefore, based on the published reports that new-onset asthma continued after NYC WTC exposures for greater than four years based on the increases in 12-month prevalence [*Time Interval Source 1*], the Administrator has determined that the best available evidence supports selecting a maximum time interval of five years for use in the evaluation of a case of an OAD for certification in the WTC Health Program.

B. Category II—Upper Respiratory Diseases

The WTC Health Program has identified chronic rhinosinusitis, pharyngitis, and laryngitis as the most commonly detected upper respiratory diseases, and observed that symptom onset for upper respiratory diseases in their NYC WTC patient population was frequently delayed by up to 6 months after response activities had ceased. [*Time Interval Source 3*]

In 2006, the WTC Responder Health Consortium published a study on a diverse group of 9,443 NYC disaster workers including first responders, recovery and cleanup workers, and volunteers who had participated in medical monitoring and received physical screening evaluations between June 2002 and April 2004. Among these workers who reported no history of respiratory illness or symptoms before the WTC disaster, 55% reported developing new upper respiratory symptoms while engaged in WTC-related work, and 44% reported upper respiratory symptoms that persisted at least up to the time of their examination, which could have been as much as 2.5 years later [Herbert et al. 2006]. Although the rate of symptoms that began while engaged in WTC-related

¹¹ An increase was also observed when compared to asthma 12-month prevalence rates reported by the Behavioral Risk Factor Surveillance System, but the difference was not as great.

work is reported, no attempt was made to ascertain whether symptoms began after WTC-related work ended, but the study does indicate that respiratory symptoms persisted for at least 2.5 years. [*Time Interval Source 1*]

The Administrator has determined that because little information is available on time intervals for new-onset of upper respiratory diseases (i.e., there is limited information from *Time Interval Sources 1-3*), selection of a maximum time interval for this category will be based on analogy to a similar health condition (*Time Interval Source 4*). The upper respiratory diseases, such as reactive upper airways dysfunction, are caused by inflammatory processes which also underlie reactive lower airways dysfunctions such as asthma. Based on the similar underlying mechanism of inflammation, the Administrator has chosen asthma as the referent health condition to support selection of a maximum time interval (see Section III.A.). [*Time Interval Source 4*] Therefore, the Administrator has selected a maximum time interval of five years for use in the evaluation of a case of an upper respiratory disease for certification in the WTC Health Program.

C. Category III—Interstitial Lung Diseases¹²

Inhaled irritant gases and fine particles that penetrate the respiratory system can affect the upper respiratory system (nose, pharynx, and throat), the larger (trachea and bronchi) and small (bronchioles), as well as the lung parenchyma (alveoli). Classically, interstitial pulmonary fibrosis can occur after inhalation of chemicals and dusts with varying latency periods ranging from months (toxic inhalation of oxidant gases and accelerated silicosis) to decades (simple silicosis, and asbestosis) [Guidotti et al., 2011]. [*Time Interval Source 2*]

Among NYC WTC responders and survivors, cases of interstitial lung disease (ILD), such as sarcoidosis [Izbicki et al. 2007; Miller 2007; Bowers et al. 2010; Crowley et al. 2010] and interstitial pulmonary fibrosis [Mann et al. 2005; Izbicki et al. 2007; De la Hoz et al. 2008a,b; Wu et al. 2010] have been reported. Numerous enrollees in the Fire Department of New York City monitoring and treatment programs were first diagnosed with sarcoid-like granulomatous pulmonary disease during the first year after the September 11, 2001 terrorist attacks and additional enrollees were diagnosed in the ensuing four years. The average annual incidence rate over these five years was significantly greater than the annual incidence rate for the 15 years prior to the September 11, 2001 terrorist attacks [Izbicki et al. 2007]. However, time intervals

¹² The American Thoracic Society/European Respiratory Society defines interstitial lung disease as a term that broadly describes a diverse collection of more than 200 lung disorders. These diseases are classified together because they all affect the tissue and space around the alveoli (air sacs), called the interstitial space. Depending on the specific disease, other compartments of the lung, including the alveoli themselves, the airways (trachea, bronchi, and bronchioles), the blood vessels, and the pleura (outside lining of the lung), may also be affected. In general, most interstitial lung disease is characterized by four manifestations: (1) respiratory symptoms such as shortness of breath and cough; (2) specific chest radiographic abnormalities; (3) typical changes on pulmonary function tests in which the lung volume is decreased; and (4) characteristic microscopic patterns of inflammation and fibrosis. <http://www.thoracic.org/education/breathing-in-america/resources/chapter-10-interstitial-lung-disease.pdf>

between WTC exposure and onset of ILD symptoms have not been described. [*Time Interval Source 1*]

The typical progression of ILDs often includes an insidious onset with a silent period with respect to pulmonary function [NIOSH 1986]. For these reasons, the incidence of these outcomes may be underestimated and may increase over time. [*Time Interval Source 2*]

The Administrator has determined that because information on time intervals for new-onset ILD symptoms among WTC populations is not available (*Time Interval Source 1*), the best information available to select a maximum time interval is the historical information on the time interval necessary for development of ILD symptoms in other cohorts with exposures analogous to WTC agents [*Time Interval Source 2*]. The Administrator has determined that at this time, the best available evidence supports not selecting a maximum time interval for use in the evaluation of a case of an ILD for certification in the WTC Health Program.

D. Category IV—Gastroesophageal Reflux Disease (GERD)¹³ Co-occurring with an Aerodigestive Disorder Identified in Category I, II, or III (i.e., Co-occurring WTC-related GERD)

The WTC Health Program has observed that the most commonly diagnosed gastrointestinal condition in enrollees is GERD. WTC-related GERD pathogenesis is primarily based upon irritant exposure mechanisms. Irritants, including stomach acid, typically produce an effect within a relatively short time period. Inflammation of mucosal surfaces in the airways and esophagus (and possibly the stomach) may be the common mechanism underlying the resulting clinical comorbidity among the WTC population [Wisnivesky et al. 2011].

Studies of the time interval for onset of GERD symptoms among the WTC-exposed cohorts were not found in the published literature (*Time Interval Source 1*). Published studies that addressed time intervals for onset of GERD after analogous exposures in other cohorts were also not found (*Time Interval Source 2*).

The Program has noted that the onset of symptoms of upper gastrointestinal disorders in the NYC WTC patient population when the patient also had a WTC-related health condition identified in Category I, II, or III was frequently delayed by at least several months after the WTC event; an upper range could not be determined.

The Administrator has determined that because little information is available on time intervals for new-onset co-occurring WTC-related GERD (i.e., there is limited information from *Time Interval Sources 1-3*), selection of a maximum time interval for

¹³ Gastroesophageal reflux disease (GERD) is defined by the American Gastroenterological Association as “a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications.” Symptoms are “troublesome” if they adversely affect an individual's well-being. Esophageal GERD syndromes are categorized as those that are symptom based and those that are defined by tissue injury [Vakil et al. 2006].

this category will be based on analogy to a referent health condition. A likely underlying mechanism of co-occurring WTC-related GERD is the irritation caused by exposure to WTC agents which also underlies reactive lower airways dysfunctions such as asthma. Based on the similar underlying mechanism of irritation, the Administrator has chosen asthma as the referent health condition to support selection of a maximum time interval (see Section III.A.). [*Time Interval Source 4*]. Therefore, the Administrator has selected a maximum time interval of five years for use in the evaluation of a case co-occurring WTC-related GERD for certification in the WTC Health Program.

E. Category V—Gastroesophageal Reflux Disease Not Co-Occurring With an Aerodigestive Disorder Identified in Category I, II, or III (i.e., isolated WTC-related GERD)

Although GERD is a common disease, its pathophysiology is complex and not well-understood. GERD develops when the mucosal epithelium is exposed for a long time to agents such as stomach acid and pepsin or is in contact with luminal agents, such as trypsin or bile acids, which are not commonly present in gastric refluxate. This leads to a visible damage of the epithelium and inflammation (erosive esophagitis) or impairment of the mucosal integrity without any sign of macroscopic alteration [Farré 2013]. [*Time Interval Source 2*]

As noted In Section III.D., WTC-related GERD pathogenesis is primarily based upon irritant exposure mechanisms which cause inflammation. When GERD occurs without a co-occurring WTC-related aerodigestive disorder, there is no evidence to support a delayed onset of GERD that is associated with WTC exposures. No studies of the time interval for onset of isolated WTC-related GERD symptoms among the WTC-exposed cohorts were found in the published literature (*Time Interval Source 1*). Also, published studies that addressed time intervals for onset of isolated GERD after analogous exposures in other cohorts were not found (*Time Interval Source 2*).

After considering the best available science, the Administrator has determined that GERD that does not co-occur with an aerodigestive disorder identified in Category I, II, or III is less likely to have a delayed onset, and a maximum time interval for isolated WTC-related GERD is substantially less than for co-occurring WTC-related GERD. However, the Administrator has also determined that the maximum time interval must account for the uncertainties in the pathophysiology and irritant effects of WTC exposures which may take some time before causing GERD. Therefore, the Administrator has selected a maximum time interval of one year for isolated WTC-related GERD for use in the evaluation of a case of isolated WTC-related GERD for certification in the WTC Health Program.

IV. Conclusion

The Administrator has selected maximum time intervals based on the best available evidence for the following five categories of aerodigestive disorders for the purpose of certification as WTC-related health conditions by the WTC Health Program.

Category I — Obstructive airways diseases (OADs) including the following health conditions: (1) chronic respiratory disorder (fumes/vapors); (2) asthma; (3) reactive airways dysfunction syndrome (RADS); (4) WTC-exacerbated chronic obstructive pulmonary disease; and (5) chronic cough syndrome. For all types of OADs certification is limited to a maximum time interval of 5 years.

Category II — Upper respiratory diseases (URDs) including the following health conditions: (1) upper airway hyperreactivity; (2) chronic rhinosinusitis; (3) chronic nasopharyngitis; and (4) chronic laryngitis. For all types of URDs certification is limited to a maximum time interval of 5 years.

Category III — Interstitial lung diseases (ILDs) including all types of interstitial lung disease as defined by the American Thoracic Society/European Respiratory Society. For all types of ILDs certification is not limited to a maximum time interval.

Category IV— Co-occurring Gastroesophageal reflux disease (GERD) (GERD co-occurring with an aerodigestive disorder in Category I, II, or III). Certification of co-occurring WTC-related GERD is limited to a maximum time interval of 5 years.

Category V— Isolated GERD (GERD not co-occurring with an aerodigestive disorder in Category I, II, or III). Certification of isolated WTC-related GERD is limited to a maximum time interval of 1 year.

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